Remarks

Claims 19 and 145-156 are pending.

Claim 145 has been amended. Support for this amendment can at least be found on page 15 lines 30-31. New Claim 157 has been added. Support for this claim can at least be found on page 15 line 12.

Claims 145-156 have been rejected under 35 § U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,393,763 (Black).

Claim 19 has been rejected under 35 § U.S.C. 103(a) as being unpatentable over Black as applied to claims 145-156, *supra*.

Claims 19 and 145-156 have been rejected under 35 § U.S.C. 103(a) as being unpatentable over Black in view of U.S. Patent No. 4,418,068 (Jones) and Jordan, *Journal of Cellular Biochemistry*, Suppl. 22, pages 51-57 (1995) (Jordan).

35 § U.S.C. 102(b) Rejection

Claims 145-156 have been rejected under 35 § U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,393,763 (Black).

The Examiner alleges "about" in the claimed dose of "about 60 mg" would "reasonably include any effective amount, including those doses recited in Black *et al.* Applicants disagree with the Examiner's characterization of "about." On page 15 lines 30-31, it is stated "[f]or example, " 'about' 60 mg would encompass 55 to 65 mg of raloxifene hydrochloride." In order to expedite prosecution, Claim 145 has been amended to include the "55 to 65" mg daily dose and new dependent claim 157 claims the 60 mg daily dose.

The Examiner has rejected claims 145-156 as allegedly being inherently anticipated by Black. The Examiner states that Black

> provides methods for inhibiting the loss of bone and are thus effective for the treatment of osteoporosis (Abstract). One of the most common types of osteoporosis is found in post-menopausal women (col. 1, lines 34-35).

And, then the Examiner states

> In the instant case, it flows from the teachings of Black *et al.* that patients being treated with raloxifene so as to inhibit bone loss will naturally have a reduced likelihood of developing breast cancer. It is clear that Black *et al.* contemplate treating postmenopausal women with raloxifene and further contemplate treating patients having osteoporosis with raloxifene (i.e., the same patient populations as instantly claimed). Because the same patient populations are being treated with the same drug, the instantly

> claimed result of such treatment would naturally occur in the patients being treated in the '763 patent.

Applicants refer to Black in Column 1 where it is disclosed that

> One of the most common types of osteoporosis is found in post-menopausal women affecting an estimated 20 to 25 million women in the United States alone. A significant feature of post-menopausal osteoporosis is the large and rapid loss of bone mass due to the cessation of estrogen production by the ovaries. Indeed, data clearly support the ability of estrogens to limit the progression of osteoporotic bone loss, and estrogen replacement is a recognized treatment for postmenopausal osteoporosis in the United States and many other countries. However, although estrogens have beneficial effects on bone, given even at very low levels, long-term estrogen therapy has been implicated in a variety of disorders, including an increase in the risk of uterine and breast cancer, causing many women to avoid this treatment.

Black, Column 1 lines 34-49. It is disclosed in Black that "although estrogens have beneficial effects on bone . . . long-term estrogen therapy has been implicated in a variety of disorders, including an increase in the risk of uterine and breast cancer." (emphasis added). Black is directed to a method for inhibiting bone loss to a post-menopausal women diagnosed as suffering from osteoporosis. Claim 145 of the instant case is directed to a "method for reducing the likelihood of incurring or developing estrogen-dependent breast cancer which comprises administering orally to a post-menopausal woman diagnosed as being in need of such therapy . . . ." (emphasis added). There is no discussion in Black about diagnosing or screening patients, who are to be administered raloxifene for osteoporosis, for breast cancer risk reduction or prevention. Applicants respectfully submit there is no teaching and no expectation in Black that women who are so diagnosed as being in need of such reduction of likelihood of incurring or developing estrogen-dependent breast cancer represent all postmenopausal women. Further, Applicants respectfully submit there is no teaching and no expectation in Black that women who are so diagnosed as being in need of such reduction of likelihood of incurring or developing estrogen-dependent breast cancer represent all postmenopausal women diagnosed as having osteoporosis. Applicants respectfully assert the present claims, therefore, do not flow from the teachings of Black, and in fact, the present claims require that any woman treated must first be diagnosed as needing treatment to reduce the likelihood of incurring or developing estrogen-dependent breast cancer. Therefore, Applicants respectfully assert that Black does not anticipate the present claims.

35 § U.S.C. 103(a) Rejections

1) Claim 19 has been rejected under 35 § U.S.C. 103(a) as being unpatentable over Black as applied to claims 145-156, *supra*.

The Examiner alleges that

> The reference does not explicitly disclose the instantly claimed administration for at least six months. However, in the absence of a showing of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to administer raloxifene for as long was necessary to inhibit bone loss as disclosed in Black *et al*. As such, because the same patient population is being administered the same active agent, it flows from the disclosure of Black *et al*. that such extended treatment will lead to a reduced likelihood of incurring or developing estrogen-dependent breast cancer in post-menopausal women.

In response to the 103(a) rejection, Applicants, therefore, incorporate by reference the discussion above for the 35 U.S.C. § 102(b) rejection and again state there is no teaching and no expectation in Black that women who are so diagnosed as being in need of such reduction of likelihood of incurring or developing estrogen-dependent breast cancer represent all postmenopausal women. Further, Applicants respectfully submit there is no teaching and no expectation in Black that women who are so diagnosed as being in need of such reduction of likelihood of incurring or developing estrogen-dependent breast cancer represent all postmenopausal women diagnosed as having osteoporosis. Applicants respectfully submit, therefore, that Claim 19 does not flow from the teachings of Black, and Black does not provide the artisan with a teaching to screen or diagnose women in need of breast cancer risk reduction. Therefore, claim 19 is not obvious over Black.

2) New ground of rejection: Claims 19 and 145-156 have been rejected under 35 § U.S.C. 103(a) as being unpatentable over Black in view of U.S. Patent No. 4,418,068 (Jones) and Jordan, *Journal of Cellular Biochemistry*, Suppl. 22, pages 51-57 (1995) (Jordan).

In response to the 103(a) rejection, Applicants, therefore, incorporate by reference the discussion above for the 35 U.S.C. § 102(b) rejection and again state there is no teaching and no expectation in Black that women who are so diagnosed as being in need of such reduction of likelihood of incurring or developing estrogen-dependent breast cancer represent all postmenopausal women. Further, Applicants respectfully submit there is no teaching and no expectation in Black that women who are so diagnosed as being in need of such reduction of likelihood of incurring or developing estrogen-dependent breast cancer represent all

postmenopausal women diagnosed as having osteoporosis. Applicants respectfully submit, therefore, that Claim 19 does not flow from the teachings of Black, and Black does not provide the artisan with a teaching to screen or diagnose women in need of breast cancer risk reduction. Therefore, claim 19 is not obvious over Black.

The Examiner states

> Jones teaches that the compounds of the invention are used as pharmaceuticals for antiestrogen and antiandrogen therapy, especially in treatment of mammary tumors (col. 2, lines 33-36) and can thus be administered in an effective dose to a subject suffering from such a condition (i.e., breast cancer) or at risk of suffering from such a condition (id. at lines 44-47).

(emphasis in original). Applicants respectfully assert that to the extent that Jones discloses "preventive" use, it is disclosed only in the secondary sense and not the primary sense. That is, Jones contemplated administering the drug to prevent the reoccurrence of breast cancer. Applicants point to Jones in Column 2:

> More particularly, the invention provides a method of alleviating a pathological condition of an endocrine target organ, which condition is dependent or partially dependent on an estrogen or on an androgen, which comprises administering an effective dose of a compound as described above to a subject suffering from such a condition or at risk of suffering from such a condition.

Jones, Column 2, lines 40-47. And, it is further stated in Jones that

> Accordingly, a most important embodiment of the present invention is a method of alleviating mammary cancers which comprises administering a compound of this invention at an effective rate to a patient suffering from or at risk of such a cancer.

Jones, Column 37, lines 61-65. To put these two disclosures in context, Jones states

> The effect of the compounds of this invention is described as alleviating the pathological conditions, to indicate that complete cure of the conditions cannot always be expected, but that use of an effective dose of the compounds will benefit the subject by causing at least some regression of the condition. When the compounds are used preventively, as in a subject who has suffered from an occurrence of mammary fibrocystic disease and is at risk of further occurrences, the compounds will prevent such occurrences or, at least, lessen or delay the severity of their effects.

Jones, Column 37, lines 16-26 (emphasis added). Furthermore, the disclosure in Jones to support the breast claim were all animals directed to the treatment of existing cancers. This disclosure is Test 6 and is titled "Tests Against DMBA-Induced Tumors." Jones, Column 33, line 60 to

Column 35 line 39. Therefore, Applicants assert that the disclosure in Jones contemplates the use only to prevent the reoccurrence of breast cancer.

The Examiner states that Jordan asserts

> the biological rationale of using antiestrogens for the prevention of breast cancer. It this regard, Jordan states that it is known from laboratory and clinical studies that antiestrogens protect bone and prevent rat mammary cancer (Abstract) and that a potential beneficial side effect of raloxifene to prevent osteoporosis in postmenopausal women may be a reduction in breast cancer risk (id.). In this regard, the author teaches that rather than selecting women to treat with an antiestrogen to prevent breast cancer (with the added advantage of reducing their risk for osteoporosis and coronary artery disease), it is now possible to consider using safe agents to treat all postmenopausal women to prevent osteoporosis and coronary artery disease, but with the added advantage of preventing breast cancer (page 55, left column).

Jordan makes this assertion in the context of administering raloxifene at a daily dose of 200 and 600 mg:

> Preliminary clinical studies using 200 and 600 mg raloxifene daily in several hundred postmenopausal women demonstrate that the higher daily dose will effectively lower cholesterol and reduce circulating osteocalcin levels [50].

Applicants refer to the reference Buzdar et al (listed in Form 1449). Buzdar discloses that fourteen patients with disseminated breast cancer with primary or secondary resistance to tamoxifen were treated with raloxifene HCl at a daily dose of 200 mg. In the Introduction of Buzdar, the authors state that raloxifene had higher affinity for the estrogen receptor than trioxifene and tamoxifen. The authors state that they evaluated trioxifene mesylate in estrogen receptor positive patients and they found that trioxifene had comparable antitumor activity to tamoxifen. They also state that in a few patients, who previously had responded to and then failed to respond to tamoxifen, were treated with trioxifene and showed objective response. For raloxifene HCl, Buzdar reported in the Abstract that "[t]here were no complete or partial responses and 1 patient showed a minor response," and that "[t]hese data illustrate that [raloxifene HCl] did not have significant antitumor activity in patients previously treated with tamoxifen therapy." (emphasis added). The authors concluded by stating that "[raloxifene HCl] did not show any antitumor activity in this study and no further evaluation of this drug is recommended." (emphasis added).

One of ordinary skill in the art would not be provided with a reasonable expectation that raloxifene HCl would be effective to prevent breast cancer after reading Buzdar. One of ordinary

skill in the art would not be provided with a reasonable expectation that raloxifene HCl would be effective to prevent breast cancer in a daily dosage range of 55-65 mg or 60 mg. Even as late as 1995 Jordan was only willing to speculate that ". . . clinical studies using 200 and 600 mg raloxifene daily in several hundred postmenopausal women demonstrate that the higher daily dose will effectively lower cholesterol and reduce circulating osteocalcin levels." One of ordinary skill in the art would not find motivation from Black in view of Jones and Jordan that would teach or suggest that raloxifene HCl given in dosages of from 55-65 mg/day or 60 mg/day would be effective in preventing breast cancer in postmenopausal women diagnosed as being in need of such therapy. Therefore, Applicants respectfully assert that Claims 19 and 145-156 are not obvious over Black in view of Jones and Jordan.

Respectfully submitted,

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June 10, 2009